

SEVERE GLYCOGEN STORAGE DISEASE TYPE IIIa IN THREE SIBLINGS: LACK OF RESPONSE TO DIETARY INTERVENTIONS.

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ABSTRACT

Objectives To assess varying dietary regimes on the clinical course of three siblings with GSD type IIIa.

Methods We studied three siblings:

a) male age 6 b) female age 4 and c) a female age 2 years.

We reviewed retrospectively the clinical notes, laboratory results including creatine kinase CK, AST, ALT and dietary interventions over an 18 month period.

Results All three siblings manifested growth retardation, hepatomegaly, and cardiomyopathy. On a dietary regime of high protein (average 4.5 g/kg/d) with high CHO (average 15 g/kg/d), the median CK levels (n: 20-155 u/l) were in a: 3854 u/l (r: 1585-7984), b: 1903 u/l (r: 119-3651) and c: 757 u/l (r: 457-1576). On a regime of increased CHO (average 15.5 g/kg/d), the median CK levels were in a: 3139 u/l (r: 1447-6463), b: 2479 u/l (r: 636-4549) and c: 494 (r: 292-918). There was no significant difference in results with different interventions. The three patients have some degree of hyperinsulinism.

Conclusions: This case series illustrates the persisting challenges of satisfactory treatment of severe presentations of GSD IIIa.

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Background

Glycogen Storage Disease (GSD) type III (MIM 232300) is caused by deficiency of glycogen debranching enzyme (AGL). In GSD IIIa AGL is deficient in both liver and muscle. The symptoms include varying degrees of hypoglycaemia, hepatomegaly, growth retardation, and skeletal and cardiac myopathy. In patients with muscular involvement muscular weakness is usually minimal during childhood, but can become severe after the third or fourth decade of life, as evidenced by slowly progressive weakness and wasting. Dietary management of GSD III consists of avoidance of hypoglycaemia with frequent CHO supplements. Uncooked cornstarch, as a slow-release CHO has been used to prevent hypoglycaemia. A high protein diet may also be effective in preventing hypoglycaemia as gluconeogenesis

is intact in these patients. Over treatment of GSD may cause symptomatic hypoglycaemia secondary to hyperinsulinism.

Aims and Methods

The objectives of this study were to assess varying dietary regimes on the clinical course and the biochemical profile of three siblings with severe GSD IIIa. We studied three siblings a) male age 6, b) female age 4 and c) female age 2 years. The clinical notes were reviewed retrospectively with special reference to the initial presentation, growth assessment, and clinical findings including hepatomegaly. The laboratory results including CK, AST, glucose, insulin, and C peptide were reviewed. Different dietary interventions with varying CHO and protein intake were analyzed.

Case Reports

We report on three siblings with GSD IIIa. The parents are second cousins. The family is members of the Traveller Community which is an industrial/nomad group. A paternal uncle also has GSD IIIa.

Table. 1 Median of Creatinine Kinase on Different CHO and Protein Concentrations

	Case I	Case III	Case III
Median Creatine kinase on (CHO 15 g/kg/d and protein 4.5 g/kg/d)	3845u/l (r:1585-7940)	1903 u/l (r:119-3651)	757 u/l (r:457- 1576)
Median Creatine kinase on (CHO 15.5 g/kg/d and protein 6.5 g/kg/d)	3139u/l (r:1447-6463)	2479u/l (r:636- 4549)	494 u/l (r:292-918)

The first sibling JD is a 6 year old boy who presented initially at the age of 4 months with hypoglycaemia, hepatomegaly and growth retardation. He had a cervical myelomeningocele repaired in the neonatal period. The diagnosis of GSD IIIa was based on the finding of a red cell glycogen of 789 $\mu\text{g/g}$ Hb (n: 10-20) and undetected lymphocyte AGL activity. JD has experienced recurrent respiratory tract infections and bronchiactasis. Cardiomyopathy was diagnosed at the age of 2 years. An ECG and Echocardiography showed bilateral ventricular hypertrophy. He manifested hyperinsulinism at 3 years of age with an insulin level of 25 u/l and C peptide of 320 u/l when the blood glucose was 2.3 mmol/l.

The most recent clinical assessment indicated a weight above 97th centile and height at 25th centile. Abdominal examination revealed hepatomegaly of 14 cm below the costal margin. JD was admitted to the metabolic ward 26 times with either acute infection or for dietary management.

PD is a 4 year old girl who was diagnosed with GSD IIIa as a result of high risk newborn screening. The red cell glycogen was 656 $\mu\text{g/g}$ Hb. (n: 10-20) and AGL was not detected. She developed cardiomyopathy at 18 months of age. ECG and Echocardiography showed bilateral ventricular hypertrophy. PD developed hyperinsulinism at 2 years of age. The insulin was 128 u/l and C peptide was 95 u/l when the blood glucose was 2.3 mmol/l. A recent clinical assessment demonstrated a weight above the 97th centile and height at 10th centile. The liver edge was 10 cm below the costal margin. PD was admitted to the metabolic ward 22 times.

Table. 2 Median AST and ALT Levels

	Case I	Case II	Case III
Median AST (n:0-30)	252 u/l (r:133-954)	431 u/l (r:160-874)	230 u/l (r:94-950)
Median ALT (n:0-30)	325 u/l (r:201-1182)	575 u/l (r:278-1060)	277 u/l (r:125-650)

GD is a 2 years old girl who was diagnosed with GSD IIIa in the early neonatal period. The red cell glycogen was 338 $\mu\text{g/g}$ Hb. (n: 10-20) and AGL was not detected. Recent examination demonstrated a weight above the 97th centile and height at 25th centile. The liver edge was palpable 8 cm below the costal margin. An ECG revealed left ventricular hypertrophy and Echocardiography confirmed hypertrophic cardiomyopathy with asymmetrical septal hypertrophy. GD developed hyperinsulinism with an insulin level of 278 $\mu\text{g/l}$ and C peptide of 2013 $\mu\text{g/l}$ when blood glucose was 2.4 mmol/l. GD was admitted 8 times to the metabolic ward.

Eighteen month of management were reviewed. Forty blood tests for AST, ALT, and CPK levels were performed on each of the cases. Different dietary interventions were tried to achieve reasonable metabolic control. All cases received high CHO diet, mainly complex CHO such as uncooked cornstarch. Protein intake was high, average 4.5 g/kg/d increased to average 6.5 g/kg/d. All

cases received continuous nocturnal gastric feeding. All cases were on diazotize.

Discussion and Conclusions

In glycogen debranching enzyme deficiency glycogenolysis is impaired; however, endogenous glucose production from non-carbohydrate substrates is intact. Compared to GSD type I, where both glycogenolysis and gluconeogenesis is blocked, a frequent supply of carbohydrates is usually less compelling. Although the prognosis of this GSD IIIa is thought to be relatively benign, recent reports suggest that patients with myopathy or cardiomyopathy may have a fetal outcome. Here we present three cases with GSD IIIa with profound AGL deficiency and persistent evidence of elevated CPK and myopathy despite differing aggressive dietary regimes (high CHO and protein regimes). These three siblings exhibit very significant early complications associated with GSD III, namely growth retardation, liver dysfunction, myopathy and cardiomyopathy. All three manifested evidence of secondary hyperinsulinism during the 18 month study period as previously noted by Lee and colleagues. The mutation has not yet been elucidated in this family.

In conclusion this case series illustrates the persisting challenges of satisfactory treatment of severe GSD IIIa.

References

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